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(54) Title: SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING METFORMIN AND METHOD OF ITS PRODUCTION

(57) Abstract: Monolithic pharmaceutical composition containing metformin hydrophobic polymer and/or other hydrophobic material. Process of producing a sustained release of the composition that includes granulating metformin hydrochloride and hydrophobic polymer and/or other hydrophobic material by hot melt granulation or by extrusion and drying the granulated product.

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING METFORMIN AND METHOD OF ITS PRODUCTION

Field of the Invention

The present invention relates to sustained release pharmaceutical preparations containing metformin hydrochloride which provides sustained release of metformin hydrochloride over a prolong period of time and a method of producing it.

Metformin hydrochloride is a well known biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which is widely used as oral antihtperglycemic agent in the management of noninsulin dependent diabetes mellitus (NIDDM).

Metformin hydrochloride being a highly water soluble drug (>300 mg/ml at 25°C), leads to the difficulty in making a sustained release dosage form.

Marketed preparations available earlier with 850 mg dose of metformin hydrochloride having label of retard tablets (Glucophase RTM retard) have not been able to demonstrate any advantage in a limited volunteer trials. This probably attributable to poor choice of polymers and low dosage, desired for sustained action.

US patent 5,955,106 by Moeckel, J. describes the process of making metformin hydrochloride 850 mg retard tablet containing hydrocolloid forming retarding agents and further control of release provided by film envelop. It

however does not provide any justification for using 850 mg dose of metformin hydrochloride for delayed release preparation and the expected release rates from such compositions. This patent also does not give any in-vitro and in-vivo data to support its claims. Literature survey indicates metformin hydrochloride has only 40% to 60% bioavailability with high renal clearance. Hence the dose 850 mg may be insufficient to achieve therapeutic plasma concentration, around 1 µg/ml for a sufficient period of time and might require to take such tablets twice or thrice a day.

WP patent 99/47128 by Timmins et al describes a biphasic controlled release delivery system for metformin hydrochloride with inner solid particulate phase and outer solid continuos phase utilizing hydrophilic and hydrophobic polymers. These tablets are hydrodynamicaly balanced and swells upto approximately three times its dry size following hydration However it is well documented that in supine position the tablet escapes through the pylorus of the stomach after administration, which may deteriorate the tablet's in-vivo performance. Also volume desired to maintain floating of the tablet is never enough in the stomach except in fed condition. Hence making such system is doubtful with reference to its performance. Another major limitation of this patent is about dosage of the metformin hydrochloride and formulation. For instance, examples cited provides formulation of 500 mg metformin hydrovchloride with tablet weight of approximately 1.0 gm . Hence restricting to the use of low dose sustained release tablets of 500 mg or slightly more only and making it obligatory to take two tablets of 500 mg each time to provide sustained action.

The present invention is based on the scientific calculation of dose of metformin hydrochloride desired, based on the data available from in-vivo studies which are well documented in the scientific literature. The model used here is based on the mathematical equations provided by Dobrinska and Welling (1975) which gives fairly accurate calculations about loading dose and maintenance dose for achieving sustained release effect.

The dose of metformin hydrochloride is calculated by considering the following pharmacokinetic values from the literature.

Plasma concentration Cmax = 1.02 µg/ml

Elimination half life t 1/2 = 6.2 hours.

Volume of disribution Vd = 275 litrs.

Renal clearance = 552± 139 Litrs/min.

Total clearance = 1300 ml/min.

Using Dobrinska and Welling model, the calculated loading dose is 283 mg and maintenance dose is 759 mg and the total dose is 1040 mg of metformin hydrochloride for achieving sustained release effect for 24 hours.

The object of the present invention is to prepare palatable and swallowable pharmaceutical preparation containing as high as approximately 1.0 gm metformin by suitable technology showing demonstrable release rate and facilitated in-vivo absorption for the desired period. The emphasis is to develop simple monolithic system composed of hydrophobic polymers and other excepients with improved kinetics of extended release dosage forms and with highest possible content of active substance and the simplest method of producing it.

The monolithic sustained release system of the invention is a homogeneous system composed of active drug in an amount within the range of 60 to 90% by weight, preferably 70 to 80% by weight, and one or more hydrophobic polymers or one or more other type of hydrophobic materials. In an amount within the range of about 15 to 40% by weight, preferably 20 to 30 % by weight based on the weight of the active substance.

Hydrophobic polymers which may be employed for the monolithic sustained release system in the present invention include, but not limited to stearic acid, glycerylmonostearate, glyceryl behenate, glyceryl monooleate, glyceryl palmitostearate, microcrystalline wax, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, hydrogenated castor oil, tristearin, waxes, polyethylene powder, polyvinyl chloride, shellac, rosin, and the like. Where the mixtures of the hydrophobic polymer will be employed in weight ratio to other hydrophobic material within the range of about 1: 0.01 to 1: 5 , preferably about 1 : 0.3

The pharmaceutical compositions according to the present invention can be used to produce compressed tablets of any shape, preferably oval shape and can be additionally provided with film coat of commonly used hydrophilic coating polymers. The film envelop used cane a taste neutralizing film forming agent to which dies can optionally be added can be used for elegance. The proportion by weight of the film envelop relative to the final tablet is in the usual range of 0.5 to 4.0% by weight preferably 1.0 to 1.5% by weight. Film formers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch, cellulose derivatives and the like.

The monolithic composition according to the present invention can also be used to produce compressed slugs and filled into capsules.

Auxiliary substances which may be employed for monolithic sustained release system in the present invention include, binder, like polyvinyl pyrrolidone, gelatin, gum acacia, Klucel EF (hydroxypropyl cellulose), carboxymethyl cellulose sodium, etc.; Where as the glidants include, but not limited to colloidal siliconedioxide, talc, starch, and the like; lubricants include, but not limited to magnesium stearate, zinc stearate, and the like

The pharmaceutical dosage form according to the present invention such as tablet, apart from active drug and hydrophobic polymers and or hydrophobic materials may contain 1.0 to 15 % by weight of a binder, preferably 3.0 to 10 % by weight ; and upto 2.0 % by weight of glidant preferably 0.5 to 1.0 5 by weight; and upto 2.0 % by weight of lubricants preferably 0.5 to 1.0 % by weight ; each in relation to the tablet weight.

In the present invention the pharmaceutical composition, such as tablets are produced by dry mixing of active substance and optionally further auxiliary substance and granulating this mixture with hydrophobic polymers and or other hydrophobic materials by hot melt granulation technique using jacketed rapid mixer granulator at a temperature 40 to 120 °C, preferably 60 to 80 °C. This is followed by gradually cooling the granulate mass to the room temperature with continuos mixing. The resulting mass is further granulated with aqueous or organic solution of the binder followed by drying and converting it into 30 µm to 2.0 mm granules, preferably 100 µm to 1.0 mm by

milling and sizing. Subsequently appropriate other pharmaceutical auxiliary substances are admixed with the sized granules.

In the present invention the pharmaceutical composition, such as tablets are also produced by dry mixing of active substance, optionally further auxiliary substances, hydrophobic polymers and or another hydrophobic materials and binder in extruder. This mixture is extruded at a temperature 40 to 120 °C , preferably 60 to 90 °C in a simple extruder used for injection molding of plastics, followed by extrusion of the melted homogeneous mass with gradual cooling to room temperature and converting into 30 to 2.0 µm to 2.0 mm granules, preferably 100 µm to 1.0 mm by milling and sizing. Subsequently appropriate other pharmaceutical auxiliary substances are admixed with the sized granules.

The composition produced in this manner is subsequently processed in the usual manner to produce pharmaceutical dosage forms, such as e.g. Compressed into tablets or filling of pressed slugs into capsule. The tablets can be coated with a film using the standard coating processes and methods such as conventional coating pan or fluid coating process.

The sustained release tablets according the present invention release metformin hydrochloride in a controlled manner which is suppose to provide an effect over a time period upto 24 hours, preferably over 18 hours as per the calculations.

Useful metformin sustained release formulations as per the invention shows the following in-vitro drug release characteristics when tested in gastric fluid pH 1.2 for first hour and then in phosphate buffer pH 6.8 USP.

Time	% Release
1	38 – 45%
2	50 – 55 %
3	62 – 68 %
4	70 – 75 %
5	80 – 85 %
6	85 – 90 %
7	91 – 95 %
8	96 – 100 %

Example 1 :

225 gm of stearic acid was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 70°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone were dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1310 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	40 %
2	55 %
3	65 %
4	75 %
5	82 %
6	89 %
7	95 %
8	99.5 %

Example 2 :

225 gm of stearic acid , 1000 gm metformin hydrochloride, 60 gm of shellac and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1310 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows

Time (Hrs)	% Release
1	42 %
2	57 %
3	68 %

4	77 %
5	84 %
6	90 %
7	96 %
8	100 %

Example 3 :

250 gm of glyceryl mono stearate was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 80°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone were dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1335 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	39 %
2	52 %
3	61 %
4	72 %
5	80 %
6	88 %
7	94 %
8	98 %

Example 4 :

175 gm of polyethylene powder , 1000 gm metformin hydrochloride and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1200 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	48 %
2	54.2 %

3	64 %
4	73.4 %
5	82 %
6	90.3 %
7	96 %
8	99.7 %

Example 5 :

160 gm of polyvinyl chloride powder , 1000 gm metformin hydrochloride and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1185 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	42 %
2	53.1 %
3	62,5 %
4	72 %
5	80 %
6	85 %
7	94 %
8	98.8 %

Example 6 :

230 gm of hydrogenated castor oil was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 70°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone was dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1315 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	41 %
2	53 %
3	66 %
4	74.9 %
5	83 %
6	91 %
7	96.2%
8	100 %

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1. Moeckel, J., Gabel, R., Woog, H., [1997] , U.S. Patent 5,955,106.
2. Timmins, P., Vyas, K., [1999] , World Patent WO 99/47128.
3. Noel, M., (1980) , Jounal of International Biomedical Information and Data (IBID), 1 (1) , 9 – 20.
4. Kenneth, C., Ralph, A. D., (1998) , Diabetes Reviews, 6 (2) , 89 – 131.
5. Nancy C. Sambol, Jaine Chaing, Michael O'Conner, Chui Y. Liu, (1196), J. Clin. Pharmacol., 36 , 1012 –1021.
6. Physician Desk reference, Edition 58, (2000), Medical economic company Inc. NJ 07645-1742, Glucophase® , page 831–835.

CLAIMS :

1. Monolithic pharmaceutical composition comprising metformin hydrochloride as the active substance and hydrophobic polymer and or other hydrophobic material.
2. Composition of claim 1, wherein the sustained release dose for metformin hydrochloride is at least 1000 mg.
3. Composition of claim 1, wherein at least 74 % by weight of the composition is metformin hydrochloride.
4. The pharmaceutical formulation as defined in claim 1, wherein the hydrophobic polymer and or hydrophobic material is selected from the group consisting of Fatty acids, Fatty alcohols, Fatty acid esters, Hydrogenated oils, waxes and natural resins.
5. Composition of claim 4, wherein the hydrophobic polymer and or hydrophobic material comprises stearic acid, glyceryl monostearate, glyceryl behenate, glyceryl pamitostearate, glyceryl monooleate, microcrystalline wax, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, hydrogenated castor oil, tristearin, shellac, rosin, polyvinyl chloride powder, polyethylene powder, and the like.
6. Composition of claim 1, further comprising about 3 to 10% by weight binder, up to 0.5 to 1.5% by weight glidant and up to 0.5 to 1.0% by weight of the lubricant.
7. Composition of claim 1, wherein pharmaceutical composition is tablet.

8. Process of producing a sustained release metformin hydrochloride composition of claim 1 which can be compresses comprising :

   i) Granulating metformin hydrochloride and hydrophobic polymer and or other hydrophobic material by hot melt granulation or by extrusion.

   ii) And drying the granulated product.

9. Process of claim 8, wherein the aqueous or organic solvent used in the granulation step contains a binder.

10. Process of claim 8, including the further step of compressing the dried granulated product into tablets.

11. Process of claim 10, including the further step of coating the tablet with a film envelope for taste neutralization.

12. Process of claim 10, wherein the compacted product further includes up to 1.5% by weight of lubricant, upto 1% by weight of glidant, and up to 4.5%by weight of binder.

13. The pharmaceutical composition according to claim 1 which releases metformin hydrochloride in a controlled and reproducible manner right from start and in the duration of minimum 8 hours.

14. The pharmaceutical composition of claim 1, used as oral antihtperglycemic agent in the management of noninsulin dependent diabetes mellitus (NIDDM).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/01404

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 37/52; A61K 47/30, 9/20, 9/22, 9/28
US CL : 514/635, 772.3; 424/464, 465, 468, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/635, 772.3; 424/464, 465, 468, 474

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/47128 A1 (BRISTOL-MYERS SQUIBB COMPANY) 23 September 1999, See entire document.	1-14
Y	US 5,922,769 A (BARELLI et al.) 13 July 1999, See entire document.	1-14
Y	US 6,011,049 A (WHITCOMB) 04 January 2000, See entire document.	1-14
Y	US 6,099,859 A (CHENG et al.) 08 August 2000, See entire document.	1-14
Y	US 6,099,862 A (CHEN et al.) 08 August 2000, See entire document.	1-14
Y	US 6,117,451 A (KUMAR) 12 September 2000, See entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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